PRESENTATIONS AT THE NCAB MEETING DECEMBER 1, 1982

Acquired Immune Deficiency Syndrome: Dr. Chabner, DCT, NCI, Bethesda
Dr. Curran, CDC, Atlanta

Dr. Chabner: The Acquired Immune Deficiency Syndrome (AIDS) is a problem that first came to our attention about a year and a half ago. The morbidity and mortality report of the CDC in July of 1981 mentioned an outbreak of Pneumocystis carinii pneumonia and Kaposi's sarcoma in otherwise well patients and these were two very unusual diseases which one does not normally find in otherwise healthy people and it was an alarming finding. The other aspect of this which was quite alarming was that these cases were occuring among homosexuals, primarily male homosexuals in New York, Los Angeles, and San Francisco, and this alerted us to the possibility of an unusual new form of cancer and also an opportunity to study a disease from the prodromal symptoms, the early stages where there was no cancer recognized to the point where cancer was developing. It offered an opportunity to try to understand the process of carcinogenesis and perhaps identify an etiologic agent in this population. Now let me tell you something about the clinical course of this disease and its pattern of occurrence and clinical presentation and then Dr. Curran will tell you something about the epidemiology.

The AIDS syndrome--Acquired Immune Deficiency Syndrome--is basically an acquired failure of T-Cell mediated lymphocyte function. The lymphocytes in the body are divided into two types; T- and B-Cells. The T-Cells are responsible for cell mediated immunity and defects in T-Cell function, which we know can occur in other settings, for example, with immunosuppression related to organ transplantation therapy or inborn errors of immune

the fact that they had decreased helper T-Cells. They have normal B-Cell numbers and normal numbers of. suppressor T-Cells, so that the abnormality seems to be, at least this point, localized to the abnormal function of the helper T-Cell population.

As I mentioned, the first cases were seen in homosexual males in New York. These cases have been traced back to probably presenting about four years ago, although the first written reports appeared in the literature only about a year and a half ago. There are now cases in most major U. S. cities and foreign countries. In some of these instances the patients in foreign countries have known contacts, homosexual contact, with people in New York or other American cities. There are fewer cases in number in foreign countries then in the United States. Primarily the cases have occurred in New York, Los Angeles, and San Francisco, those are the largest numerically. At this point when the slide was made we had 600 known patients that had the disease, now the number is closer to 800 patients, and Dr. Curran will bring us up to date on this. Of the patients known to have the disease, about 40 percent have died at this point, but many have not really lived through the course of their disease and we expect that the fatality rate is actually much higher than this.

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This shows you the incidence figures that can be traced back to the time of presentation. Going back through the requests for medicine to treat Pneumocystis carinii in pneumonia, its been possible to trace a few cases back to 1978, there has been an increasing number ever since. The projected number for 1982 here is 300 and probably will be more than that. The latest case accrual rates are between three and four per day now and ...

(audience question not audible)

Its Acquired Immune Deficiency Syndrome

(audience question not audible)

Yes they do, they have infections and/or this cancer syndrome. I'll describe the clinical syndrome in a little more detail in just a minute.

(question only partially audible... what you're talking about is 800 people who have autoimmune deficiency disease, (Dr. Chabner: Yes) which shows the ... of this disease (Dr. Chabner: characteristics) of this ...disease

Dr. Chabner: No these all have clinical disease, these are patients, they're not simply people that have...

(Discussion inaudible)

Dr. Chabner: We will talk about that in just a moment. There is a very large background probably of patients with compromised immune function who are not now sick, but we think at risk.

(Discussion inaudible)

Right, the syndrome manifests itself, the common denominator is this defect in T-Cell function, but it may manifest itself either with infection or with various types of cancer, most commonly Kaposi's sarcoma, or both, with various mixtures of the two. The common denominator that I mentioned, the metropolitan areas that I've mentioned, and this population is a very sexually active population with many contacts per year and it seems that the people that get the disease are drawn from a population, a sub-population, that have a very high level of sexual activity. Another affected group are intravenous drug users. Most of these have been young Blacks or Hispanics who are heterosexual and live in New York or the New Jersey, adjacent New Jersey area. Some have been women as well as men, so here we have primarily males, here we have both women and male heterosexuals.

Question: Which drugs Bruce?

Dr. Chabner: Usually heroin addicts, intravenous drug users, and this is an important point. The third group that had been found to have this AIDS Syndrome are Haitian immigrants to the United States. They have in general no history of homosexuality or drug abuse, they have had both Kaposi sarcoma and the overwhelming infections, Pneumocystic carinni or atypical tuberculosis. There have been a few cases reported in hemophiliac males, these are people that get repeated blood transfusions, blood product transfusions I should say; and then a smattering of other cases including otherwise totally normal individuals a few of whom have been identified as recent transfusion recipients; and there have been a few cases, which Dr. Curran can discuss, of children of women known to have had the AIDS Syndrome.

Next slide please

The major presenting symptoms of these patients have been fever, malaise, wasting, and diarrhea. These complaints may go on for months and cannot be traced to any specific cause. Many of the patients will present with oral fungal infections or candidiasis. On presentation they'll be found to have a lymph node enlargement. In most of these patients when these lymph nodes are biopsied they just show lymphoid hyperplasia but no lymphatic malignancy although some do have lymphatic malignancies. We'll talk about them in a minute. They all have a profound defect in cell mediated immunity, that is they don't respond to skin test antigens and they have this inversion of the T-Cell helper suppressor ratios. Many of them at presentation will have opportunistic infections which are not found in normal populations. These are infections which occur in immunocompromised hosts. The most important of these infections are Pneumocystis carinii; fungal infection, some unusual funguses; cytomegalovirus. Almost all of these patients have

cytomegalovirus in their positivity in their blood or in urine; many of them present with herpes simplex infections of the mouth or anal region; and some of the patients in addition have cancer and we'll talk about the types of cancer they have in a moment, most of them are Kaposi sarcoma or lymphoid malignancy.

Can I have the next slide

The clinical course of these patients is a progressive wasting syndrome, loss of weight, fever, sequential infections, these infections that I've mentioned can occur. Several of these infections can occur in series; as one is treated a new one arises or the old one recurrs. About 40 percent develop neoplasms, especially in the homosexual male population, these are primarily Kaposi sarcoma, which is a tumor of the endothelium found primarily in skin but also disseminating to other organs. These patients also develop B-Cell lymphomas of the Burkitt type. These are relatively unusual tumors and they seem to be occurring in a very high incidence in these patients as well, and some patients develop squamous cell carcinomas of the head and neck as well.

Question: Could you give a percentage for those three?

Yes, the majority of them get Kaposi's sarcoma, of the cancers that they develop about 95 percent are Kaposi's. There have been perhaps 10 to 12 cases of Burkitt type lymphomas reported and we don't really have incidence figures for squamous cell carcinoma although we know that isolated examples of these are occurring in these patients. The patients all have profound immuno suppression and may develop severe leukopenia later in their course. At presentation most of them have a normal white count, but the helper T-Cell population is profoundly depressed. This course is usually inexorable and over a period of months or years leads to the patients demise.

Question: Bruce, two questions, is it the Kaposi's like U.S. or Mediterranean Kaposi's or more like African Kaposi's. It sounds like its the kind that kills people, (Dr. Chabner: Yes) and from George Alexander a fair number of Africans Kaposi's...

Dr. Chabner: These cases are more of the agressive variety which metastasizes to the lymphnnodes and to organs and its not like the type that occurs in older males of Mediterranean extraction which is a relatively benign disease.

Question: OK, so this, and do you have a lead time from the time of their habituation, or whatever you want to call it--exposure's what you call it, until the time of the diagnosis and determining the different diseases....

Dr. Chabner: No, the interesting thing is that this disease was not seen in this population in the young male homoxsexuals and in the intravenous drug users until the last three years, so we don't really...

Question: Does it go back as far as the ... history on any of these..

Dr. Chabner: No, you can't really relate it to when they began to live the homosexual life style. In other words, there's not an incubation period we can establish.

Question: All my experience is that I expect squamous cell carcinoma may have a much longer period of development rather than a lymphoma or something else, that's why I asked.

Dr. Chabner: I don't really know. You know there's not alot of published information about this squamus carcinoma, so I really don't know how intimately they are involved with this, the ones that were very sure about as being involved with the lymphomas and Kaposi's sarcoma.

Question: So squamous carcinoma may be occurring at no greater instance than in the general population?

Dr. Chabner: I don't think that's the case. I think its occurring in unusual populations, occurring in young males who are non-smokers and non-alcoholics, so there seems to be a real association. Actually there's another tumor called a cloacal carcinoma which is occurring in the same population, independent of the AIDS Syndrome, a very unusual tumor again, higher incidence than normal, but probably not associated with the AIDS Syndrome. So there are several types of disease.

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The types of infections associated with this syndrome primarily Pneumocystis carinii a very rare infection in nonimmunusuppressed patients. Its found in 60 percent in the AIDS patients and its often unresponsive to the conventional treatment or it recurs after its initial occurrence. The other striking thing thats occurring is avian tuberculosis. This is an atypical tuberculosis infection which is often systemic found in overwhelming numbers in the bone marrow for example and very difficult to treat, very unresponsive to chemo-therapy. A number of other very unusual kinds of infection are occurring in this population.

Next slide:

The malignancies I mentioned, Kaposi's, its not the indolent variety that one finds in the elderly Mediterranean population, its usually a highly aggressive metastatic tumor and it occurs in about 40 percent of the patients.

Next slide:

This is the fatality rate as related to the data diagnosis and as you can see the longer follow up period is the higher the mortality rate up to

close to 90 percent of the patients who were diagnosed in the 1979 to 1980 period. So we feel that the longer these patients are followed, the more of them really will die of the disease. Etiology, I'll leave this to Dr. Curran to discuss in more depth. There are alot of ideas that have been suggested including exposure to nitrites, other drugs, the cytomegalovirus itself may be a cause, some unknown venereal transmitted agent. We know that sperm is an immunosuppressant so that it may be that that may play a role, and alot of other ideas. The one that seems to be most likely, Next slide, is that its a virally caused agent. Its spread is very reminiscent of hepatitis B in that it effects homosexuals in very high frequency as does hepatitis B, it effects intravenous drug users, it effects hemophiliacs, people that receive numerous transfusions. No virus has been found yet, no hepatitis like virus, or any other virus, but there is very active research on this aspect of the disease. The other things that suggest that its a virus is the clustering, the fact that you can find chains of contact between patients who get the disease, and the mother to child transmission which I've talked about. So the major conclusion; its a blood born virus. How do the Haitians fit in, well we know that the homosexuals, particularly those in the New York area take vacations in Haiti and we speculate that maybe this is an endemic virus from Haiti which has been transmitted to the American homosexual population and from there to other affected populations. Next slide:

The treatment has been quite unsatisfactory, chemotherapy, single agents, and indolent disease produce a high response rate but a fair complication rate, but most patients have the aggressive form of the disease which has been treated with combination chemotherapy with adriamycine, bleomycine, and velban. Although there is a high response rate, there's a very high

complication rate. These drugs only add to the immunosuppression that the patients get and there's no evidence that this is really beneficial in the long run for these patients. There may be more beneficial results in treating the lymphoma that occurs because it is highly drug responsive.

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Interferon seems to have a possible role here in that Memorial Hospital has treated 12 patients and has obtained two complete responses in patients with Kaposi's. These patients are off therapy for a very short periods of time. Three partial responses in seven patients with stable disease, but these patients all died eventually. The interesting thing about interferon is that possibly it might correct the immune deficiency as well as treating the underlying cancer. But this is only speculation, there's no evidence at this point that immune deficiency can be corrected with interferon.

Next slide:

Other possible treatments, antiviral agents, where we don't know what the virus is and we don't really have effective treatments for systemic viruses, for most systemic viruses. Thymosin has been suggested as a way of stimulating helper cell function. I don't think there has been any experience using thymosin up to this point. There have been several attempts at bone marrow transplantation in an attempt to restore the lymphocyte population. These have been unsuccessful, have not been takes of the bone marrow, and of course these patients have overwhelming susceptibility to infection which complicates this tremendously.

Next slide:

Now, we've mentioned the populations that get the disease; who is at risk? Well, there are some interesting statistics lately. Studies of otherwise normal male homosexuals have shown, one study from New York showed that 80

percent have an abnormal helper to suppressor ratio. Are these patients at risk of getting the AIDS Syndrome? These are clinically well patients. We know that a significant fraction of the male homosexual population in New York and San Francisco have chronic lymphadenopathy. Are these patients likely to develop the infection and tumor? We don't know, but these are serious questions. Hemophiliacs who recieve blood transfusions are probably at risk, there have been something like seven or eight cases now in hemophiliacs, there are 1,500 in the United States and this presents a potential target for the disease; possibly blood product recipients, although there is much less evidence here to worry about. There's a little evidence for family member transmission, Dr. Curran might speak to that. Sexual contacts possibly; and health care personnel possibly, people who are taking care of these patients, no cases yet reported though in hospitals. I guess there have been an isolated one or two in hospital workers but none in doctors or nurses.

We can skip this, this is just--next slide

This slide only showed the incidence of the abnormal heler to suppressor ratio in otherwise normal homosexuals.

What is the NCI doing about this? When we first were informed of this we had a workshop on this and during the year supplemented certain grants of institutions in the cities where they were seeing these patients--$200,000. Dr. Adamson's Division supplemented support contracts in environmental epidemiology. We know that a considerable amount of grant work, and this is just an estimate, was re-directed towards this disease because of its importance. We estimate about $1 million was put immediately into research in this area. In addition there is a major intramural laboratory and clinical effort to

understand the disease, between us, efforts being between us and the Allergy and Infectious Disease Institute.

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The other thing that we've done is in conjunction with Dr. Adamson's Division we've put out an RFA, a request for proposals to study the disease, its epidemiology, etiology, and treatment. We've put $250,000 into this and Dr. Adamson's Division put $1 million into it. These responses are now being evaluated and will be out on the street, awarded, in the next two months, so we feel at that point there will be more than $2 million invested in this in NCI funds.

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OK, that concludes my presentation, maybe I could briefly ask you if there are any questions about the clinical syndrome, I'd like to get Dr. Curran's presentation.

Response by someone: I want to commmend you on this very interesting presentation, thats all I have to say.

Speaker #1: We're worried about the timing now and Dr. Gallo said he'd be glad to come back any time ..... thats it, if there isn't any objection. We can finish up this and hear Dr. Gallo at the next board meeting. I know alot of you have planes in about an hour from now and you're looking jittery.

Speaker #2: I certainly regret that we don't get to hear Dr. Gallo today.

Speaker #1: But I do want to mention though, for coming over, as I mentioned before, two weeks ago Dr. Gallo was the co-recipient of the Albert Lasker Medical Research Award for what is a very high achievement that we'll now hold up for the Board.

Stand up Doctor and lets give him a big round of applause.

Dr. Chabner: Are there any questions about this before Dr. Curran's presentation?

Question: I want to ask to ask you sir if there is any evidence of of this in any other parts of the world? What about Haiti?

Dr. Chabner: There have been cases identified as Kaposi's sarcoma in Haiti, a cluster of cases that one dermatologist has seen there. The level of medical care there is such that I don't think we have reliable figures on the incidence in Haiti, we don't have much information, maybe Dr. Curran can tell us more.

Question: inaudible

Dr. Chabner: No, not in this... they are all in the populations that I have indicated.

Inaudable comment

Dr. Byrd: Bruce, there has been some anecdotal information thrown out and I have no idea how responsible this information is that some observers are seeing AIDS in very sexually active heterosexuals.

Dr. Chabner: I don't know anything about that, Dr. Currans is our expert on the relationship of the disease to sexual activity so we'll ask him.

Dr. Hickey: I believe there is another population that has Kaposi's sarcoma and its a very interesting occurance and also a high frequency as you go down the list of neoplasms of Squamous Carcinoma and I have reference to the group of patients who have undergone renal transplantation and I don't know whether you included that in your other group or not.

Dr. Chabner: Yes. I mentioned that in the beginning, that they are one of the antigenic(?) populations where they are receiving immuno suppression.

Dr. Hickey: But the interesting point is that if they, at least a few of the patients according to Isreal Penn (?) if they are taken off their suppressive therapy that the Kaposi's sarcoma disappears.

Dr. Chabner: That's right. Yes. They also have a high incidence of B Cell Lymphomas too like this population and of course pneumocystis and opportunistic infections so this disease really mimicks what we see in chemically immunosuppressed patients.

Speaker: To follow on with that, its my impression that the the lymphomas and the renal transplant patients were primarily in the brains.

Dr. Chabner: Thats right. They have an unusually high incurrence of histiocytic lymphomas in the central nervous system, that is true, but the histology of the tumor is a diffuse histiocytic lyphoma or a large cell lyphoma. This is more like a Burkitt lymphoma, both are B cell tumors.
Inaudible comment from audience
Dr. Curran tells me there have been two or three cases of Reticulum Cell Sarcoma or DHL in the brain in the AIDS patients.

Dr. Mustofi: Dr. Chabner, did you know the incidence of Kaposi is very high in South Africa? Do you have any sort of information among the black populations in South Africa?

Dr. Chabner: I spent two weeks in South Africa last year in black hospitals primarily and I didn't see any.

Speaker: There is a high population in Tanzania, it is a fertile group to compare. They have all three symptoms, one of which is very the aggressive disease, of course the obvious study is to compare the immunologic status of those patient.

Speaker: And then cost us separately then to have.....

Speaker: Hasn't this been around for a long time in small quantities in elderly Jewish men and its just been a slow fomenating thing that doesn't really cause ... I thought .....

Dr. Chabner: Kaposi's yes, AIDS no. And in these people, the elderly Jewish people that got this disease, didn't have abnormal T-cell function and the rest.

Speaker: Well, it seems to me we had a presentation by Dr. Levine somewhere along the line that he raised that issue that its been around a long time in certain aging populations but not with this virulence and not with all these other .... things .

Dr. Chabner: Thats true. If there are no further questions can I turn the program over to Dr. Curran.

Dr. Curran: Thanks a lot Bruce. It's really a pleasure for me to be here and its has been a real pleasure for me to have work with the National Cancer Institute in the past year and a half. We people at CDC seldom get a chance to take the road most traveled by and get a chance to work with the people who are dealing with the problems that kill most Americans. I would like to introduce, reintroduce, the topic that Bruce introduced of a new syndrome and like every ... think that we are in the first couple years of the recognition of a disease thats going to probably be with us

forever. You will hear a lot about this over the next decade or so I think. I think this is an important problem and in case Dr. Goble has to leave I would like to let him know that there's probably another virus out there that needs to be discovered. This is a new syndrome and it's newly recognized and I think to put it in some perspective, the question asked about renal transplant recipients is the same. If you think of these risk groups as having far, far too much cyclosporin A, and then you watch what happens to them, without anybody being able to take away that immunosuppression then you have an idea of what sort of awaits many of the risk groups that have been identified thus far. Kaposi's sarcoma, of course, is a cancer that occurs in perhaps 200 or 250 cases per year according to the NCI SEER registries, but 80 percent of these cases occur in people--is that right Jim?--80 percent of these cases occur in persons over age 50, and its generally a really indolent skin cancer as opposed to an aggressive disease, whereas 95 percent of the patients in this epidemic have been under age 50. The diseases that we talk about, and the ones I will talk about here, are marker diseases, they are diseases that are extremely rare in normal populations and when they occur in a 100-fold excess incidence in a given population they are easily recognizable. Even serious illnesses like squamous cell cancers, which are fairly common, even in young populations would not be picked out for example if they came into an oncologist just because the person happened to be gay and it would be very difficult to prove that there is an excess incidence of a given type of more common cancer. The other thing that is very interesting to me about Dr. Penn's work in renal transplant patients is that Kaposi's sarcoma and reticulum cell sarcoma of the brain, which has been re-named since I learned about it, are cancers that are so rare that its very easy to pick them out and then all of the

other excess incidence of cancer renal transplant patients that are grouped together in squamous cell carcinoma. When you look at the literature and break it down by type its very difficult to pick out exactly what the relative risk is with each particular cancer type. The other thing is that the incubation period post transplant is, I think, earliest for Kaposi's sarcoma, something like a year and a half to two years. Presumably, post immunosuppression, then Kaposi's sarcoma comes up with the median time of occurrence of the other squamous cell cancers is several years, I think, I may be wrong--for five years Peter?--. So that we are in the beginning of an epidemic and this is the first cancer to occur in large excess and its recognizable easily because its so rare.

Let me see the first slide please.

The underlying problem here, remember, is a severe profound immunosuppression and most of the patients present with a cachexia and wasting or with Kaposi's sarcoma, or in some cases both. They're not difficult to recognize syndromes, they're 35 year old, prosperous, previously healthy men who come in looking like they're going to die, spend the next six or seven months in the hospital, run up a hospital bill of $100,000 to $150,000 and then die. So its not something that's missed, each case is a grand rounds case in its individual hospital and they are diseases that are previously recognized. Let me say one more thing about pneumocystis pneumonia, that's a fairly rare illness that we have fairly good tabs on because we're the only dispensers of pentamidine isothionate at the time, at the current time. Pentamidine isothionate is the sort of second drug, second line drug following the use of bactrum for pneumocystis pneumonia and is used in probably about 50 percent of cases around the country either because of bactrum failure or because of toxic or allergic reactions to bactrum. Since all of the

pentamidine is requested from CDC, and this has been true since 1967, we are able to go back and look at our pentamidine requests and see whether pneumocystis occurs in persons without underlying disease or immunosuppressive therapy. In fact from 1967 to 1980 there was only one questionable case out of thousands of requests of a case of pneumocystis pneumonia requiring pentamidine in persons without underlying disease. In 1980 there were nine such requests in retrospect, all in gay men. In 1981 forty percent of the requests, some 70, were in persons without underlying disease with AIDS, and now about 65 percent of the pneumocystis pneumonia in the Country we estimate is occurring in perons without underlying disease or cancer immunosuppressive therapy. So there is more pneumocystis, there's actually more pneumocystis in New York City in gay men then there are in cancer patients in the entire Country. Ninety five percent of the pneumocystis I think at Memorial Sloan Kettering Cancer Center is in homosexual men without cancer. So, it gives you an idea that its a fairly dramatic illness, not something that would be missed easily. Our functions have been in the area of surveilance, epidemiologic studies, and laboratory studies and I'd like to spend most of the time talking about surveilance and epidemiologic studies and perhaps speculate a little bit on where this syndrome will probably go. Surveilance has been important and largely now is passive except for some active components, from our point of view, in establishing the incidence of the disease trends in identification of new epidemiologic patterns. It was recognized in 1980-1981 that there was an excess of illnesses that I'll describe in homosexual men and probably as early as that in intravenous drug users. In mid 1981 it seemed to be occurring in Haitians and most of them had recently entered the United States, that is, within the past 3 or 4 years. In July of 1982 in the Morbidity and Mortality

Report, reported three cases of pneumocystis carinii pneumonia and severe T-Cell immunosuppression among persons with hemophilia A, who were persons with severe hemophila A requiring large amounts of factor A concentrate to replace their clotting factors. Hemophilia patients were predicted to be the group to acquire this syndrome if it could be acquired by blood because of the large number of donors that contribute to their blood products each year. Its been estimated that as many as 50,000 donors contribute to one hemopheliac's care each year, there are about 15,000 hemopheliacs in the Country. Well, since that July 27th report in the MMWR all three of those hemopheliacs have died and five more cases have been identified in the United States in four different states, the patients with pneumocystis pneumonia or other severe immunosuppressive disorders, making about eight cases now diagnosed in the past 11 months. There is some preliminary information suggesting that there are some mild immunologic abormalities similar to what Dr. Chabner described in gay men also occurring in the hemophelia population and also lymphadenopathy and thrombocytopenia seems to be occurring in this population, so the syndrome is disturbingly similar in hemophelia patients to that occurring in drug addicts and gay men.

New Slide

The case definition for the remainder of the slides includes biopsy proven Kaposi's sarcoma, or culture proven life threatening opportunistic infections only. Its the serious end of the spectrum that we would consider a definite case rather then any speculative cases that might be less specific for this syndrome. So, the illnesses are either Kaposi's sarcoma or a variety of infections which I will show you that are associated with immunosuppressior such as congenital immune deficiencies, other malignancies than Kaposi's sarcoma, or when therapy with immunosuppresive agents is removed. There

are an additional 100 patients or so mostly gay men or drug users with nephrotic syndrome type complications who have been on steroid therapy who probably are part of the syndrome but we exclude them because of their steriod therapy prior to diagnosis.

Next Slide

This is the list of the life threatening opportunistic infections. The one that is easiest to monitor, from our point of view, and easiest to confirm as unusual is pneumocystis carinii pneumonia under protozoa, but in addition, disseminated toxoplasma infections and a very very rare enteric pathogen called cryptosporidium, a previous animal pathogen has plagued these men. The cryptosporidium gastroenteritis is essentially nontreatable, results in loss of two to four liters of diarrhea per day for several months until the patients die. In terms of viral infections disseminated cytomegalovirus infection, very extensive herpes simplex virus infections, and progressive multifocal leukoencephalopathy due to polio viruses have been documented in these gay men. Very commonly, the patients with Kaposi's sarcoma or the opportunistic infections have thrush or esophageal candidiasis which is very unremitting to therapy often. Cryptomenengitis, disseminated spurgelosis, disseminated histoplasmosis, etc. etc. every zebra from the medical text book that you remember is present in these cases and they generally get them sequentially; they recover from one infection and they get another one. The recurrence from Pneumocystis is something like 20 percent.

New Slide

If you will look at the old iceberg of every new disease, every time a syndrome is recognized the very tip of it is recognized, in fact Morris Kaposi himself after he changed his name from Cohn, Morris Kaposi himself, when he discovered the syndrome back in 1870 described disseminated

Kaposi's sarcoma leading to death and in the parentheses he says this is probably the tip of the iceberg , I don't think its exactly how he said it but its something like that. We know that there are other things occuring. Dr. Ziegler, previously of the National Cancer Institute, has reported four cases of diffused undifferentiated non-Hodgkins lymphoma seen in gay men in San Francisco in ten months since he moved out there. The entire bay area is expected to have one case in the entire population per year. At least 20 percent of gay men who have been tested in New York City have unexplained generalized lymphadenopathy, the median duration of about twelve months, which often waxes and wanes and may be accompanied by recurrent fever, malaise, or just general nonspecific symptoms. Most of these people have some aborations in their immunological function. A paper in the Annals a few months ago described autoimmune thrombocytopenic purpura thought to be a female dominated disease occuring also in large numbers in gay men who are immunocompromised in New York City. This has been a common problem among the patients with Kaposi's sarcoma, unexplained drops in the thrombocyte platelet count. Anywhere from 20 to 80 percent of gay men who have been tested in a variety of studies in San Francisco, Atlanta and New York city have been found to have abnormalities in cellular immune functions in vitro. It is not clear what this means, at the very worst it means that all of these people are incubating a more serious illness since they are a few years younger than the Kaposis patients and the AIDS patients. At the very best it means that it is totally unrelated but due to some other virus that they may have acquired.

Next Slide

If you look at the incidence of the disease from the point of, and this includes, Pneumocystis, Kaposi's sarcoma, and both, and I apologize for the cut off here. These numbers range from about 8 to 23 and should go up like

so. If you look at when the disease was first reported in July of 1981 you can see that about 90 percent of the cases have been reported and diagnosed since that time. This is the onset since the multi-diagnosis.

New Slide

If you look at the month of onset of symptoms in these patients, however, you see that from June of 1981, when the first cases were reported, there appears to be an increase in incidence in cases that were prior to the time of the first reporting. In fact we did extensive surveilance in eighteen major metropolitan areas at this time and were unable to uncover any disease in any areas other than New York and California during that surveilance period.

Next Slide

This is the report of a slide made two weeks ago where there were 732 cases of definite AIDS. Again these serious life threatening illnesses which are the tip of iceberg occuring in the United States. You can see that about 30 percent of patients have Kaposi's sarcoma alone. A full 7 percent have both Kaposi's sarcoma and Pneumocystis Pneumonia. 50 percent have Pneumocystis without Kaposi's sarcoma, where nearly 100 patients have other life threatening infections. As you might expect if you have both it is worse, if you have the opportunistic infections your survival appears to be worse than the Kaposi's sarcoma alone.

Next Slide

The overall mortality rate in reported cases is 40 percent. Unfortunatly that represents an optimistic account of the survival in that 70 percent of the cases have been reported and have been diagnosed in the past 10 months and the twelve months survival rate in the cases reported to us is about 40 percent or about 60 percent mortality. If you look at the case fatality rate

by time, by 6 months period, you can see that once you get beyond a year its fairly gloomy.

New Slide

A study done by Dr. Bateek (?) and others in New York City, where she reviewed 80 charts of patients with Kaposis sarcoma and 80 charts of persons with opportunistic infections only, and calculated a life table analysis of the expected survival of the patients, the median survival in the charts she reviewed for Kaposi's sarcoma was 16 and one half months. The median survival for the patients with the opportunistic infections was six months. Predicted two year survival rate of the patients with the opportunistic infections was zero, and the two year survival rate for Kaposis sarcoma predicted would be 25 percent. I would take this to be a most pessimistic outlook. I think this is very close to being accurate here. This is probably pessimistic in that many of the early cases that were early recognized only in the disseminated version were probably included up here.

Next Slide

But it's a bad illness and the occurrence of cancer is related to the immunosuppression but you can't stop the immunosuppressive agents, that's the problem. If you look at age distribution, 85 percent of the cases have been in persons under age 45, 60 percent are white, 20 percent black, 6 percent Hatian black, and about 12 percent hispanic.

New Slide

One of the striking things is the unusual geographic distribution. I think we have come to take it for granted but about 97 percent of the cases reported in the entire world are in the United States and half of them are in New York City. This is a disease of very, very high incidence in a very, very small

number of people. If you look at selected groups of gay men in New York City, there is some preliminary evidence that the incidence may be as high as 3,000 per 1,000,000 in this group and the excess mortality is something like 50 percent above normal mortality in this group thus far. The incidence in New York City is about 12 times that in the United States. If the incidence were the same as here there would be about 10 or 11 thousand cases now in the United States, if the incidence were the same as it is in New York City. The incidence in New York City and in San Francisco is very high.

New Slide

95 percent of the cases are occuring in men and as of the last week there were 775 cases in the United States and about 60 reported from outside the United States, 45 women and the remainder men. About 80 percent of the men are homosexual or bisexual with approximately 115 heterosexual men with about 35 whose sexual orientation is unknown. That is unknown to us, it is presumably known to them. (laughter)

New Slide

People asked me why it is unknown and I said I think we did pretty well getting 95 percent, that is better than most employers do. Epidemiologic investigations began with, from our point of view, in June with extensive interviews of 30 living cases. A rapid survey of popper usage, poppers of nitrite inhalents are stimulants that are thought to be inhaled and thought to have some sexual potential both in relaxing the anal sphincter and creating quite a rush. As a matter of fact they are sold. They're illegal. It is illegal to buy amyl nitrite of course without a prescription. It is readily availible but it is illegal and isobutyl and torbutyl nitrites are sold as room oderizers not for inhalation with such names as Rush and Locker Room and Bolt and names like that. Then I would be saying more about a case

controlled study of AIDS among homosexual men in New York and California and cases outside New York and California, interviews of heterosexual cases in clusters. In addition we have been involved in studies of chronic generalized lymphadenopathy in New York City which demonstrated an increased trend of lymph node biopsies for benign reasons in selected hospitals and had been involved in a variety of studies in Hatians and hemopheliacs which I won't comment on.

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Our case control study case definition involved living homosexual and bisexual men with Acquired Immune Deficiency Syndrome either pneumocystis or Kaposis without underlining illness in persons who are voluteering or who were not too ill to be interviewed. At the time this was performed in October/November, 1981 we interviewed 70 percent of the living patients in the United States and 80 percent of the living patients in New York and California and compared those interviews to controls from a variety of sources who were matched for age, sexual orientation, race, city, and interviewer.

New Slide

There was a 21 page questionnaire and 25 or 30 serologic tests that were done in each case, in each control. There were 346 items in the questionnaire, 125 variables which were subjected ----- to analysis put in a conditional logistic progression model and these are the things that popped out as those things that are significant from that model. The most significant variable discriminating cases from controls, and controls were picked from either VD clinics or from private physicians who saw patients primarily for VD, was the number of male sex partners per year. On average, cases in our study had an average of 61 sex partners in the year preceeding the onset of their illness and an average for their sexual lifetime of about 60 per year compared to

only 25 to 27 per year for a homosexualy active controls from these clinics. A median lifetime number of sexual partners was about 1,150 in this group and aproximately 500 in each of these two and a third control groups. The proportion of sexual partners from bath houses was also a significant discriminating difference. The cases were more likely to get them there. That can be explained, however, perhaps based on the availability of larger numbers of partners. Cases begin their regular sexual activity with men somewhat earlier than did controls.

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Additional varibles which were significant but did not contribute as much in the equation to the difference between cases and controls included the number of different street drugs ever used in the lifetime. Cases had used six, where controls averaged four. The lifetime use of inhalents...

Question: Can I ask you a question on that-that would seem like an enormously difficult item to come up with. Most people in fact have no idea what the drugs are that they are using on the street or I should say have very little idea except for some very sophisticated illegal users. Isn't that correct? They are sold all sorts of things with all sorts of names and in fact we know almost nothing about the pharmacology of these things. By interviewing them we obviously know about the pharmacology if we take the drug and analyze it.

Dr. Curran: Well, you are right, and that's even true of nitrites and poppers. There have been studies published related to amyl nitrite versus ? nitrite and things like that. They don't really know necessarily what they are using under the circumstances but we had about three pages of questions on drugs and we asked them under their street names usually.

This varible is a very crude one obviously but its ever usage of one of some thirty or forty different things that were asked and the median number was six for cases. Now that includes things like marijuana which almost all of them know, herion, cocain, qualudes, a lot of these things are known. Also, gay men perhaps are more sophisticated than many other people who use drugs on a regular basis and the average case was a college graduate here, so there is a little more knowlege. But, I agree with you generally that it would be very difficult to sort out any, to make any biologic imputations from this. It does point out that the life style was slightly different in some way, lifetime use of nitrites and poppers and the more days they were used by cases than controls. Fisting refers to insertion of the fist into the anal canal and insertive fisting and in terms of once, at least once in the past year, cases had done that more often than did controls. This was an interest to us primarily because of the finding that hepatitis A is more common in selected gay men and that some perhaps enteric pathogen might be facilitated by these particular practices. This was a significant difference but was not a uniform sexual practice. Rimming or analingus refers here to insertion of the tongue into the anal canal or rectum and that was done more frequently by cases than controls but as you see not a large difference.

New Slide

Other things that were interesting, Italian ancestry was more common among cases than controls and this was entirely among the patients who has Kaposis sarcoma as opposed to those with opportunistic infection. This is consistant with the previous findings that Italians and Ashkonazi Jews more commonly get Kaposis sarcoma and also consistant with the finding of DR5 excess among patients with Kaposis sarcoma compared to controls since Italians have the gene frequency almost double that of the general population of

DR5. So, it's nice to see that the old things fit in to some extent. That is my interpretation, others may have a different interpretation. It isn't neccessarily good because if you don't get Kaposis and you have this you may end up with something worse. The history of syphilis was twice as common in cases than controls and this was validated by positive treponemal test for syphilis in 70 percent of cases compared to 35 percent of controls. The treponemal test used was a microhemoglutination treponemal palitive test. It's very simular in terms of functions to the FTAABS test, a test which measures past syphilis as well as present syphilis. We think this is a marker of promiscuity and a validater of promiscuity difference rather than a specific risk factor. Similarly non B hepatitis history was more common in cases than controls and in fact 85 percent of cases had positive antibody titer to hepatitis A, compared to 50 percent of this control group and 55 percent of that control group. So that is another validater of promiscuity and perhaps some mode of aquisition clue.

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The study that was done in Los Angeles, California, further lends support anyway to the postulate that this might be a sexually transmitted etiology among homosexual men. Of the first nineteen cases of AIDS reported from Los Angeles, Dr. David Olivoc and William Darryl from our group, along with Michael Gotlieb from UCLA and others, were able to interview intensively 13 of the original 19 patients or their live-in lovers or consorts and were able to obtain from those 13 men a listing of people they had had sexual contact with during the five years prior to their illness onset. Of course they were not able to obtain all of the names, and in two patients they were not able to obtain any names since the patients had died. Suffice it so say that in 9 of those 19 cases, in 9 of the 13 that they were able to

interview they were able to show that 9 of the cases had had direct sexual contact with another case of AIDS somewhere in the United States. In fact there was one case outside of California who had had direct sexual contact with four cases in Los Angeles, none of whom knew each other and were separated by some 75 miles in terms of their living residence. This made us think that this was probably not occuring by chance although it can't be ruled out. If you assume that there are hundred thousands of homosexual men in Los Angeles in order for this to occur randomly the chances would be 1 times 10 to the -12th. Take that as a logical assumption though, it is conceivable that if these people all knew each other, none of them did, that it might be more likely.

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Further interview of this out of California case, who has lived now in two coutries and four different states, we found that we were able to get a list of some 72 sexual partners whose names he had, out of a number of 750 that he claimed to have had during the past three years. He is a living man with Kaposi's sarcoma. He is still out there. He had sexual contact with 8 other cases of Kaposis sarcoma, pneumocystis pneumonia, or dissemenated C&V infection. Actually there's a diffuse histeocytic lymphoma up here also among those 72 partners.

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If you look at this and if you want to think about incubation periods from the point of view of when he had sexual contact with these people, both from the point of view when he might be infectious and how long it would take to recognize illness beyond exposure, he had contact with the people about 9 to 22 months prior to the onset of their symptoms. Five of the patients that he had sexual contact with that developed illness were during 1980. Of the

250 partners he had here during 1982 two of them have been diagnosed with Kaposis sarcoma or AIDS. So the average peroid of time between contact and onset of illness is about 14 months.

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That's certainly a very loose figure because it's based on a number of hypotheses. It's important to recognize that incubation period from the point of view of how long it takes for the illness to spread to other populations, to increase in frequency, to double, to affect other people, and I think if we're thinking of implications of other groups being affected we have to be patient and think of the few years down the road. We're getting a jump on this thing, all of us. If you look at the persons who are heterosexual you see that there is a big difference between heterosexual patients and the homosexual patients in terms of the percentage of intravenous drug usage while the gay men often give a history of qualude and marijuana usage and even snorting cocaine very, very few have every used intravenous heroin or intravenous cocaine and even when they did it was generaly a once experimental nature. In contrast three-quarters of the heterosexual men and those of unknown sexual orientation and three-fifths of the heterosexual women with AIDS are hard line intravenous heroin addicts or have been intravenous heroin addicts.

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We interviewed 33 of these heterosexual men and women and just to show you the contrast between the groups, the 50 homosexual men had a mean years of school of 15 years whereas the heterosexual men and women had about 11. Now, the average income was almost $20,000 per year in homosexual men, where the average income in these two groups reported income was nothing, it wasn't nothing, none were over $20,000 I'm sorry, but the average income is pretty

low (laughter). Its pretty hard to buy heroin with nothing, right. Most of these patients had been married, and most of these hadn't. So these are not, these are ___(?)___ groups of people. Seventy-five percent of these patients were white. About 25 percent of these groups of patients were white, these are more likely to be Black and hispanic. Fifty percent of the cases in gay men in the United States are occurring in New York City. Ninety percent of the the cases in I.V. drug users are occurring in New York City, which would be consistent with the hypothesis of a highly mobile gay population and very much less mobile drug addict population. If it were to effect persons receiving blood products, one would expect them to be scattered around the country based on the distribution of the particular blood product. The factory concentrate which is distributed very broadly we see 8 cases in hemophelia patients in 6 different states.

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Question: In the drug users, what is the hypothesis? Because I think most were I come from thought that was a bigger industry than General Motors for example.

Dr. Curran: The hypothesis would be, my hypothesis would be, infection a la hepatitis B via needle sharing with carriers or affected patients and in fact some preliminary interviews, some preliminary interviews of heterosexual cases that have been drug users have indicated that most of them have shared needles with gay men for example and some of them have shared needles with other cases.

Mrs. Kushner: May I ask if the gentleman with several hundred fifty partners is still out there loose or has he been put away? I mean really, is there no recourse?

Dr. Curran: We're dealing with a hypothesis that this is a transmissible agent. It's been recommended to him that he (laughter) that he (laughter) not have any sexual partners. It was recommended that he go into seclusion.

Ms. Kushner: But, there's no legal, nothing that CDC can do in a case like this?

Dr. Curran: Well, the country's been fairly, this is a philosophical remark, but I think the country's been fairly conservative about making recommendations towards people's personal lives. What do we tell surgeons who are hepatitis B surface antigen and E antigen positive, or dentists who are hepatitis B surface antigen E antigen positive? And I've got to clean my teeth, I'll tell you.

Ms. Kushner: People with TB have to go to homes in the state of Maryland.

Dr. Curran: Well, there's no definite test for this disease and there probably are many people who may be carriers of it and it's very difficult to--We'll be talking about prevention recommendations later.

Ms. Kushner: We have a good size gay community here in Washington, DC, that is quite open. Has anybody thought to find out why we don't have any kind of high incidence the D.C. gay community?

Dr. Curran: Well, Dr. Gettert(?) and Dr. Bigger from the National Cancer Institute have conducted a number of studies in cooperation with them. There are, I think, about a dozen cases in Washington and there have been a number of cases treated here at the Clinical Center from outside Washington as well. The heterosexual patients, when they were interviewed, they were found to be not promiscuous, had relatively few partners, both the men, lifetime partners in the past year.

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And the women. Subsequently we interviewed one more woman who was a prostitute and not an IV drug user and she had several thousand partners. But other than that they tend to be non promiscuous IV drug users.

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If you look at the drug history of the heterosexuals interviewed versus the homosexual men interviewed marijuana is the only drug that is really, and cocaine, are the drugs that have been commonly used by both, and cocaine here has been mostly infrequent usage of inhalant of cocaine and here it's generally speed-balling or what do you call it intravenous injection of cocaine. The other drugs that are commonly used by the gay cases or not commonly by the heterosexuals. Note here the frequency of intravenous heroin usage by these cases compared to the gay men. Nitrites were commonly used by gay men, very infrequently used and generally despised by heterosexuals.

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Cytomegaloviruses has been a virus of interest because of its previous association with Kaposi's sarcoma because its known association with cellular immune suppression in its primary infection state and because of the frequency of its sexual transmission among gay men. You can see that, however, among heterosexual cases about almost 20 percent had negative titers to cytomegalovirus and my own feeling is that it may be related to Kaposi's sarcoma as an outcome in gay men, but it probably is not the primary cause of the immunosuppression.

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So what we're left with is these groups affected thus far. Homosexual or bisexual men, 75 percent of the cases. And a really very small group of them right now. In Toronto they think this is a syndrome that's been made up by

somebody else. In New York City they really really believe it. Intravenous drug users, again, almost all in New York City. Haitians who are mostly in Miami, Montreal, and New York at this time and there's very good evidence that it's occurring in fairly high frequency in Haiti. And hemopheliacs, there are now eight hemopheliacs with definite AIDS. Another in a point of suggestion, that thrombocytopenia, generalized lymphadenopathy, and asymptomatic immunosuppression, whatever that is, is common in hemopheliacs. There are about 5 percent of the patients that fit no risk group. This is to be expected but its a very important group for us to keep handles on and we're investigating a number of suspected cases in this group right now.
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Question: You say there is a high incidence in Haiti ...

Dr. Curran: Yes...

Question: Do you know anything about the ... incidence?

Dr. Curran: We've sent some physicians to Haiti to work with uh, there's very little known about risk factors in Haiti, and its these illnesses are not illnesses that can be easily diagnosed in developing countries. Haiti is the poorest country in this hemisphere and what we know about it is that there are too large a number of cases of disseminated Kaposi's sarcoma seen by one physician in Port-au-Prince over the past three years, so we expect that that cancer is at least occurring in excess. In addition, they describe a wasting syndrome consisting of severe diarrhea, weight loss, and thrush, which is occurring predominantly in young men and young women in the 20's and 30's. A group not expected to me malnurished even in a developing country. We've done immunological studies in about 10 of these men and

they have virtually no T-lymphocytes. So we think that the acting definition of this syndrome in Haiti is probably just a cachexia leading to death type syndrome and that's probably how it would be recognized.

Question: Its a new disease thats....

Dr. Curran: Well, they claim it is but most of the doctors who claim it is have been trained in the mid 1970's in Europe or the United States and they've just gone to Haiti. My guess is that it is and that's based on very little information, but my guess is, the reason I guess that is because Haitians have been coming into the United States for the last 40 years and they've been living in, hundreds of thousands of them have been living in the New York City area supposedly for decades and it was first recognised in New York City in 1981 among persons who have only been here for a couple of years or so. The questions is whether it will spread among the Haitian population the same way it did in Haiti and that's unknown right now. If you look at the hypotheses and look at the various ones that Bruce listed, it's very interesting that we listed the same hypotheses for the most part. In term of numbers of sexual partners, it appears to be a risk factor for homosexual men but not for any of the other groups. The use of IV drugs is a risk factor here but not for the other groups and all of the hemophelia patients have been interviewed extensively, they're not homosexual, there are two gay hemophelia patients with the syndrome but we haven't included those. But, in addition, these patients are not IV drug users or homosexual men. Nitrites are used in excess only by homosexual men not the other groups. Cytomegalovirus infection is very common here, it seems to be common here but not ubiquitous and its fairly unknown how common it is here although I would expect in this group it's quite common. Exposure to sperm

should be a risk for homosexual men only and heterosexual women. But, all four groups are at extremely high risk for hepatitis B with a uniform lifetime prevalence of virtually 100 percent in virtually all groups, and now we don't think hepatitis B causes this, but the model fits so well that it makes us think what would happen if hepatitis B were dropped on the population of New York City about 1978, how long would it take to spread to other groups? What other groups would be affected? Who should come next? And I think unfortunately as we thought that way over the past year, these groups have been ticked off as the groups. This group wasn't completly anticipated. These groups have been ticked off as groups that would be the first ones and the ones to suffer the highest incidence first. So, I think we have to ask about recipients of other blood products. We have to ask about health care personnel. We have to ask about, certainly, heterosexual contacts to cases and carriers. We have to ask about transmission from pregnant women. We have to ask about lots of things that will occur and my unforunate prediction is that they will occur, they'll develop over the next decade, and that this syndrome is here to stay.

Thank you.

(from tapes of the NCAB meeting)
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